DYNAMIC VARIABLE RELEASE TECHNOLOGY

FIELD OF INVENTION

[0001] The invention relates to novel mixed release pharmaceutical formulations having one or more active ingredients, wherein the release profile of the active ingredients is controlled to maximize the effectiveness of the pharmacological action of the actives.

BACKGROUND OF THE INVENTION

[0002] This application is a continuation of and claims priority to patent application Ser. No. 10/402,858, filed March 28, 2003. Without limiting the scope of the invention, its background is described in connection with immediate and extended release formulations and combination drug therapy, as an example.

[0003] Heretofore, in this field, medications have been formulated so that they may be administered in a reduced number of daily doses. These doses must also provide drug that is released uniformly over a desired, extended period of time. Sustained or extended release pharmaceutical formulations provide a significant advantage over immediate release formulations to both clinicians and their patients because patients require fewer daily doses than their immediate release counterparts. In some cases, extended release formulation may improve therapeutic efficiency due to more consistent drug serum levels.

[0004] Various techniques have been developed to provide pharmaceutical preparations that include, e.g., a drug-containing particle with a coating layer and a pharmaceutical preparation in a continuous matrix with a drug dispersed therein, such as embedded into a rigid lattice of a resin. To achieve extended release, some pharmaceutical preparations include generally, a partially or completely insoluble matrix that in aqueous body fluids releases the drug. Alternatively, pharmaceutical preparations made of particles may be coated to provide extended release. It is believed that the release of the drug from such pharmaceutical preparations is driven by the gradient of the drug concentration resulting

from penetration of water by diffusion into the formulation. The rate of the release decreases due to a decrease in the concentration gradient and the increase in the distance of diffusion.

[0005] A sustained release formulation is also believed to help reduce side effects caused by a drug because they deliver the drug in slow, incremental amounts versus the cyclic high and low concentrations of immediate release formulations. By providing more consistent drug levels it is argued that the patient is better able to process the drug to avoid undesirable side-effects.

[0006] Sustained release formulations for the sequential or timed release of medicaments are known in the art. Generally, such formulations contain drug particles mixed with or covered by a polymer material, or blend of materials, which is resistant to degradation or disintegration in the stomach and/or in the intestine for a selected period of time. Release of the drug may occur by leeching, erosion, rupture, diffusion or similar actions depending upon the nature of the polymer material or polymer blend used.

[0007] To improve the release profile of certain sustained release dosage forms, some formulations include tablets and capsules that include a combination of an immediate release formulation and a sustained release formulation. Although the inclusion of tablets and capsules improves control over the dosing of drug levels in the blood stream in some formulations, the extended therapeutic effect may not be improved or desired.

[0008] Furthermore, every active has different solubility properties and pH dependencies that affect, e.g., its dissolution rate, and hence its bioavailability. Bioavailability may also be affected by a number of factors such as the amounts and types of additives used, its granulation and compression, surface area, mechanical shearing (e.g., by the stomach), pH, solubility of the active agent in water, the presence of food, etc. Due to these numerous factors, the specific form of the drug, its excipients, coating, pH, dissolution profile alone, and in combination, affect the manner and formulation of actives to achieve the best bioavailability profile to achieve an optimum therapeutic effect.

[0009] U.S. Pat. Nos. 4,309,404 and 4,248,857 to DeNeale, et al., disclose slow release formulations formed of a core material containing the active drug,

carboxypolymethylene, zinc oxide, stearic acid, and mannitol; a seal coating surrounding the core; and a sugar coating surrounding the seal coating. U.S. Pat. No. 4,309,405 to Guley, et al., discloses a sustained release tablet similar to that disclosed by DeNeale, et al., except that the core contains a drug, a mixture of a water-soluble polymer such as hydroxypropylmethylcellulose or hydroxypropylcellulose and a water-insoluble polymer (ethylcellulose alone or in admixture with carboxypolymethylene, hydroxypropylcellulose and the like). The DeNeale and Guley patents disclose that their compositions provide substantially zero order release of the core contained drug for about 12 hours following the first hour of administration. Thus, zero order release is only obtained after the initial surge of release of drug in the first hour.

[0010] U.S. Pat. No. 4,695,467 to Uemura, et al., relates to a sustained release tablet that includes easily disintegrable granules including: a drug, a disintegrating agent selected from the group consisting of starch derivatives, gums, cellulose derivatives and ion-exchange resins, and a water-soluble polymer selected from the group consisting of cellulose derivatives, synthetic water soluble polymers and polysaccharides. The surfaces of the granules are treated with a wax selected from the group consisting of plant or animal wax, hydrogenated oils and paraffin.

[0011] U.S. Pat. No. 6,372,252 to Blume, et al., relates to guaifenesin sustained release formulation and tablets which may comprise a hydrophilic polymer, preferably a hydroxypropyl methylcellulose, and a water-insoluble polymer, preferably an acrylic resin, in several ratios. The formulation is said to be capable of providing therapeutically effective bioavailability of guaifenesin for at least twelve hours after dosing in a human subject. The invention also relates to a modified release guaifenesin tablet that has two portions: the first portion comprises an immediate release formulation of guaifenesin and the second portion comprises a sustained release formulation of guaifenesin as described above. A two portion, or bi-layer, tablet has a maximum serum concentration equivalent to that of an immediate release guaifenesin tablet, and is capable of providing therapeutically effective bioavailability of guaifenesin for at least twelve hours after dosing in a human subject.

[0012] U.S. Pat. No. 6,462,094 to Dang, et al., relates to decongestant/expectorant compositions consisting essentially of phenylephrine tannate and guaifenesin that are effective when administered orally for the symptomatic relief of cough associated with respiratory tract conditions such as the common cold, bronchial asthma, acute and chronic bronchitis are disclosed.

SUMMARY OF THE INVENTION

[0013] It has been found, however, that the present methods fail to provide an efficacious amount of a first active ingredient in an immediate release form and a second active that is provided as an extended release formulation that takes advantage of the pharmacological effect of the immediate release active to maximize the efficiency of the delivery and pharmacological action of the second active. Yet another problem is that certain drugs affect the release profile of a second drug that is being provided in a single dose. The present invention solves these problems in the art.

[0014] More particularly, the present invention is a formulation and method of making a formulation that provides for the dynamic variable release of actives in, e.g., a capsule in which a first active packed for immediate release; and a second active, e.g., a decongestant, antihistamine, expectorant, antitussive or pain medication, is packed for extended release and in which the first active affects the pharmacological effectiveness of the second active. The first and second actives are on separate carriers. The present invention provides for a pharmacological formulation and a method of loading an active on a bead for extended release that includes the steps of adding the active onto one or more beads with an adhesive such as pharmaceutical glaze prior to or in combination with adding a sustained release coating.

[0015] The method may also include the step of loading an active into a mini-tab to be encapsulated for extended release, using a sustain release coating or erosion matrix. As such, the present invention provides a delivery system and method of providing a dual-release formulation in which a first active in a powered form and a second active in a sustained release mini-tab or sustained release bead is provided to a patient in need of a first active that acts as, e.g., an expectorant that helps release and/or break up mucus

immediately, which then improves the effectiveness of a decongestant that is needed in a long acting form. The immediate and sustained release components may be provided in a single capsule.

[0016] The present invention also addresses a growing concern for physicians as they write prescriptions for drugs: cost. While pharmacists continue to substitute generics in order to reduce cost to the patients or allow for greater insurance coverage, the effectiveness of dosing and effect has become paramount. The present invention increases the effectiveness of the individual components, thereby reducing the number of doses and increasing the therapeutic effectiveness. It may also be used to decrease dose sizes, thereby reducing costs. In one example of the advantages of the present invention, an expectorant (e.g., gauifenesin) is provided at lower doses and is made available immediately for absorption, followed by a lower dose of a decongestant (e.g., phenylephrine) which is release slowly over, e.g., about 90 minutes to about 8 hrs. This release profile makes the product more efficacious since the large amount of expectorant begins to break up mucus and the time released decongestant provides long acting decongestant activity.

[0017] One embodiment of the present invention is a capsule that includes a first active available for immediate release and a second active for extended release that is a decongestant, an antihistamine, an expectorant and/or an antitussive. The expectorant may be, e.g., gauifenesin that is compressed into a slug of between about 50 to 600 mg. The second active comprises a nasal decongestant, e.g., phenylephrine packaged as a sustained release bead, e.g., from between about 1.5 to 30 mg. The term immediate release is defined further as over 70 percent (%) release of the active or its metabolites from between about 1 minute and about 6 hours. The term extended release is defined further as release of over 60 to 90 percent of the second active between about 1 to about 8 hours.

[0018] The present invention also includes a method of loading an active on a bead for extended release that includes adding the active onto one or more beads with an adhesive and a sustained release coating prior to, or in combination with, adding a sustained release coating. The adhesive may be a pharmaceutical glaze and the addition of the

sustained release coating may be added prior to, during or after the addition of the first active. The sustained release coating is mixed with the first active and the mixture is added onto the beads. The bead may be a sugar bead or a mini-tab, which may also include an erosion matrix and one or more inactives.

[0019] In another embodiment, the present invention is a pharmaceutical composition that includes a first active that is an expectorant packed for immediate release; and a second active that is a nasal decongestant packed for extended release, wherein the first active provides productive coughs in the short-term and the second active provides long-acting decongestant activity. A pharmaceutical composition for extended release and use in the present invention may be made by loading an active on a bead by adding the active onto one or more beads with a pharmaceutical glaze, curing the active and the glaze for between about 3 to 6 hours prior to adding a sustained release coating and repeating the steps of adding active and curing the active at least three more times.

[0020] Yet another method for providing a dual-release formulation includes providing a first active having an expectorant packed for immediate release in a powder form and a second active comprising a nasal decongestant packed for extended release on a bead. These two actives are encapsulated so that the first active provides productive coughs in the short-term and the second active provides long acting decongestant activity.

[0021] In yet another embodiment, the present invention provides a time released phenylephrine bead that is formulated to provide maximum effective release over 6-8 hours. It was found that when the beads were overcoated with immediate release gauifenesin the process was not only time consuming (since building up the bead with gauifenesin had adhesion problems), but also that overcoating of the gauifenesin on the phenylephrine slowed the release of the phenylephrine to an unacceptable level. Further attempts to increase adhesion by sustain releasing both actives also resulted in a poor release profile for gauifenesin. Nevertheless, overcoating the extended release active with an immediate release active may be used with these or other actives, depending on the actives selected and the desired efficacy.

[0022] One embodiment of the present invention includes powder filling the gauifenesin and extended release phenylephrine beads into a capsule. The solution provided herein addresses the problems of dosing, effective pharmacological serum levels and cost. This process also reduces greatly the already taxed capacity on the bead room since up to about 96% of the active load would not need to go through the bead coating process.

DETAILED DESCRIPTION OF THE INVENTION

[0023] While the making and using of various embodiments of the present invention are discussed in detail below, it should be appreciated that the present invention provides many applicable inventive concepts which can be embodied in a wide variety of specific contexts. The specific embodiments discussed herein are merely illustrative of specific ways to make and use the invention and do not delimit the scope of the invention.

[0024] The present invention is based on the recognition that patients and physicians are looking to simplify the number of doses that a patient takes, improving the efficacy of drug delivery and reducing costs. The effectiveness of dosing and effect has become paramount in order to reduce cost to the patients and allow for greater insurance coverage, while improving patient compliance.

Definitions

[0025] A number of definitions are provided herein to facilitate an understanding of the present invention. As used herein, the term "enveloped pharmaceutical" means a capsule, a suppository, a gel cap, a softgel, a lozenge, a sachet or even a fast dissolving wafer. As used herein the term "carrier" is used to describe a substance, whether biodegradable or not, that is physiologically acceptable for human or animal use and may be pharmacologically active or inactive.

[0026] The term "immediate release" as used herein is used to describe a release profile to effect delivery of an active as soon as possible, that is, as soon as practically made available to an animal, whether in active form, as a precursor and/or as a metabolite. Immediate release may also be defined functionally as the release of over 80 to 90 percent (%) of the active ingredient within about 60, 90, 100 or 120 minutes or less. Immediate release as used herein may also be defined as making the active ingredient

available to the patient or subject regardless of uptake, as some actives may never be absorbed by the animal. Immediate release formulations of the active on a carrier, such as rolled or compressed beads, may be formulated such that the surface area is maximized on beads and the active is exposed immediately. The immediate release formulations may also include effervescing agents that cause the disintegration of the structure integrity of the active and carrier such that release of the active is maximized. Various immediate release dosage forms may be designed readily by one of skill in art to achieve drug delivery to the stomach and small intestine, depending upon the choice of compression, adhesive materials and/or beading.

[0027] The terms "extended release" and "delayed release" as used herein is used to define a release profile to effect delivery of an active over an extended period of time, defined herein as being between about 60 minutes and about 2, 4, 6 or even 8 hours. Extended release may also be defined functionally as the release of over 80 to 90 percent (%) of the active ingredient after about 60 minutes and about 2, 4, 6 or even 8 hours. Extended release as used herein may also be defined as making the active ingredient available to the patient or subject regardless of uptake, as some actives may never be absorbed by the animal. Various extended release dosage forms may be designed readily by one of skill in art as disclosed herein to achieve delivery to both the small and large intestines, to only the small intestine, or to only the large intestine, depending upon the choice of coating materials and/or coating thickness.

[0028] "Extended release" and "delayed release" formulations may be prepared and delivered so that release is accomplished at some generally predictable location in the lower intestinal tract more distal to that which would have been accomplished if there had been no delayed release alterations. A method for delay of release is, e.g., a coating. Any coatings should be applied to a sufficient thickness such that the entire coating does not dissolve in the gastrointestinal fluids at pH below about 5, but does dissolve at pH about 5 and above. It is expected that any anionic polymer exhibiting a pH-dependent solubility profile can be used as an enteric coating in the practice of the present invention to achieve delivery to the lower gastrointestinal tract. Polymers and compatible mixtures thereof may be used to provide the coating for the delayed or the extended release of

active ingredients, and some of their properties, include, but are not limited to: shellac, also called purified lac, a refined product obtained from the resinous secretion of an insect. This coating dissolves in media of pH >7.

[0029] The present pharmaceutical composition may also be provided in a variety of dosage forms, e.g., solution, suspension, cream, ointment, lotion, capsule, caplet, softgel, gelcap, suppository, enema, elixir, syrup, emulsion, film, granule, gum, insert, jelly, foam, paste, pastille, pellet, spray, troche, lozenge, disk, magma, poultice, or wafer and the like.

[0030] For gelcap preparations, the pharmaceutical formulation may include oils, e.g.: (1) fixed oils, such as peanut oil, sesame oil, cottonseed oil, corn oil and olive oil; (2) fatty acids, such as oleic acid, stearic acid and isostearic acid; and fatty acid esters, such as ethyl oleate, isopropyl myristate, fatty acid glycerides and acetylated fatty acid glycerides; (3) alcohols, such as ethanol, isopropanol, hexadecyl alcohol, glycerol and propylene glycol; (4) glycerol ketals, such as 2,2-dimethyl-1,3-dioxolane-4-methanol; (5) ethers, such as poly(ethylene glycol) 450; (6) petroleum hydrocarbons, such as mineral oil and petrolatum; and (7) water, or with mixtures thereof; with or without the addition of a pharmaceutically suitable surfactant, suspending agent or emulsifying agent.

[0031] For oral, buccal, and sublingual administration, the pharmaceutical composition of the invention may be administered as either solutions or suspensions in the form of gelcaps, caplets, tablets, capsules or powders. For rectal administration, the compounds of the invention may be administered in the form of suppositories, ointments, enemas, tablets and creams for release of compound in the intestines, sigmoid flexure and/or rectum. For example, when making a suppository a beeswax/glycerol composition may be used to form a body meltable suppository for transrectal or transurethral delivery.

[0032] It is contemplated that the "immediate release" active may be formulated as, e.g., freeze dried, rotary dried or spray dried powders; amorphous or crystalline powders; granules, precipitates or particulates. The immediate release active may be either free-flowing or compressed. The pharmaceutical formulation may further include, e.g., water, aqueous solvents, non-protic solvents, protic solvents, hydrophilic solvents, hydrophobic

solvents, polar solvents, non-polar solvent, emollients and/or combinations thereof. Other formulations may include, optionally, stabilizers, pH modifiers, surfactants, perfumes, astringents, cosmetic foundations, pigments, dyes, bioavailability modifiers and/or combinations thereof.

[0033] Effervescent pharmaceutical formulations are well known in the art and include, generally, an acid such as citric acid or a mono or dihydrogen salt thereof and a carbon dioxide source such as a carbonate or hydrogen carbonate alkali metal salt, such as sodium hydrogen carbonate. The acid and the carbon dioxide source do not react together when dry but combine to release carbon dioxide and an effervescent effect in the presence of water. The effervescent pharmaceutical compositions for use with the present invention may be in the form of a tablet for dissolving in water or a dispersible powder for sprinkling onto water, prior to administration. The acid and the carbon dioxide source are blended together during manufacture of the composition in the absence of water to prevent premature effervescence.

[0034] Effervescent pharmaceutical compositions may be in the form of a tablet for dissolving in water or a dispersible powder for sprinkling onto water, prior to administration. The components of the couple are blended together during manufacture of the composition. Suitable pharmaceutical formulations include effervescent tablets and sachets containing water dispersible powders. Effervescent pharmaceutical formulations according to the present invention may be prepared by blending together the granulates formed by roller compaction with other components prior to processing into, e.g., beads. Roller compaction may also be extended to include other components, such as one or more active ingredients and non-active ingredients or excipients such as lubricants, disintegrants, flavors and sweeteners. For capsule, final processing may include introducing the beads into the capsules using an encapsulation machine.

[0035] Monosodium citrate and sodium bicarbonate, are blended together and then roller compacted, in the absence of water, to form flakes that are then crushed to give granulates. The granulates are then combined with the active ingredient or drug or salt thereof, conventional beading or filling agents and, optionally, sweeteners, flavors and lubricants. The granules are then filled together under controlled ambient conditions, to

form beads or capsules, respectively. Suitable mini-tablets will have a hardness in the range 6 to 12 Kp. The hardness of the final tablets is influenced by the linear roller compaction strength used in preparing the granulates, which are influenced by the particle size of the monosodium hydrogen carbonate and sodium hydrogen carbonate. For smaller particle sizes, a linear roller compaction strength of about 15 to 20 KN/cm may be used.

[0036] The pharmaceutical composition may also be administered as a liquid suspension or solution using a sterile liquid, e.g., oil, water, an alcohol, or mixtures thereof, with or without the addition of a pharmaceutically suitable surfactant, suspending agent, or emulsifying agent for oral or parenteral administration. For liquid preparations, the pharmaceutical composition can be formulated suitably with oils, for example, fixed oils, such as peanut oil, sesame oil, cottonseed oil, corn oil and olive oil; fatty acids, such as oleic acid, stearic acid and isotearic acid; and fatty acid esters, such as ethyl oleate, isopropyl myristate, fatty acid glycerides and acetylated fatty acid glycerides; with alcohols, such as ethanol, isopropanol, hexadecyl alcohol, glycerol and propylene glycol; with glycerol ketals, such as 2,2-dimethyl-1,3-dioxolane-4-methanol; with ethers, such as poly(ethyleneglycol) 450, with petroleum hydrocarbons, such as mineral oil and petrolatum; with water, or with mixtures thereof; with or without the addition of a pharmaceutically suitable surfactant, suspending agent or emulsifying agent.

[0037] The immediate release actives of the present invention may be processed by agglomeration, air suspension chilling, air suspension drying, balling, coacervation, coating, comminution, compression, cryopelletization, encapsulation, extrusion, wet granulation, dry granulation, homogenization, inclusion complexation, lyophilization, melting, microencapsulation, mixing, molding, pan coating, solvent dehydration, sonication, spheronization, spray chilling, spray congealing, spray drying, or other processes known in the art. The extended release actives may be provided in the form of a minicapsule, a capsule, a tablet, an implant, a troche, a lozenge (minitablet), a temporary or permanent suspension, a pellet, a bead, a pill, a strip or a sachet.

[0038] The pharmaceutical composition and/or the solid carrier particles can be coated with one or more enteric coatings, seal coatings, film coatings, barrier coatings, compress

coatings, fast disintegrating coatings, or enzyme degradable coatings. Multiple coatings may be applied for desired performance. Further, some actives may be provided for immediate release, pulsatile release, controlled release, extended release, delayed release, targeted release, synchronized release, or targeted delayed release. For release/absorption control, solid carriers can be made of various component types and levels or thicknesses of coats, with or without an active ingredient. Such diverse solid carriers can be blended in a dosage form to achieve a desired performance. The compositions may be formulated for oral, nasal, buccal, ocular, urethral, transmucosal, vaginal, topical or rectal delivery, although oral delivery is used mostly.

[0039] When formulated as a capsule, the capsule can be a hard or soft gelatin capsule, a starch capsule, or a cellulosic capsule. Although not limited to capsules, such dosage forms may be further coated with, for example, a seal coating, an enteric coating, an extended release coating, or a targeted delayed release coating.

[0040] The term "enteric coating" as used herein relates to a mixture of pharmaceutically acceptable excipients that is applied to, combined with, mixed with or otherwise added to the carrier or composition. The coating may be applied to a compressed or molded or extruded tablet, a gelatin capsule, and/or pellets, beads, granules or particles of the carrier or composition. The coating may be applied through an aqueous dispersion or after dissolving in appropriate solvent. Additional additives and their levels, and selection of a primary coating material or materials will depend on the following properties: resistance to dissolution and disintegration in the stomach; impermeability to gastric fluids and drug/carrier/enzyme while in the stomach; ability to dissolve or disintegrate rapidly at the target intestine site; physical and chemical stability during storage; non-toxicity; easy application as a coating (substrate friendly); and economical practicality.

[0041] Dosage forms of the compositions of the present invention can also be formulated as enteric coated delayed release oral dosage forms, i.e., as an oral dosage form of a pharmaceutical composition as described herein that uses an enteric coating to effect release in the lower gastrointestinal tract. The enteric coated dosage form may be a compressed or molded or extruded tablet/mold (coated or uncoated) containing granules, pellets, beads or particles of the active ingredient and/or other composition components,

which are themselves coated or uncoated. The enteric coated oral dosage form may also be a capsule (coated or uncoated) containing pellets, beads or granules of the solid carrier or the composition, which are themselves coated or uncoated.

[0042] The coating may also contain a plasticizer and possibly other coating excipients such as colorants, talc, and/or magnesium stearate, which are well known in the art. Suitable plasticizers include: triethyl citrate (Citroflex 2), triacetin (glyceryl triacetate), acetyl triethyl citrate (Citroflec A2), Carbowax 400 (polyethylene glycol 400), diethyl phthalate, tributyl citrate, acetylated monoglycerides, glycerol, fatty acid esters, propylene glycol, and dibutyl phthalate. In particular, anionic carboxylic acrylic polymers usually will contain 10-25% by weight of a plasticizer, especially dibutyl phthalate, polyethylene glycol, triethyl citrate and triacetin. Conventional coating techniques such as spray or pan coating are employed to apply coatings. The coating thickness must be sufficient to ensure that the oral dosage form remains intact until the desired site of topical delivery in the lower intestinal tract is reached.

[0043] Colorants, detackifiers, surfactants, antifoaming agents, lubricants, stabilizers such as hydroxy propyl cellulose, acid/base may be added to the coatings besides plasticizers to solubilize or disperse the coating material, and to improve coating performance and the coated product.

[0044] Immediate release coating of solid carriers is commonly used to improve product elegance as well as for a moisture barrier, and taste and odor masking. Rapid breakdown of the film in gastric media is important, leading to effective disintegration and dissolution. Eudragit RD100 (Rohm) is an example of such a coating. It is a combination of a water insoluble cationic methacrylate copolymer with a water-soluble cellulose ether. In powder form, it is readily dispensible into an easily sprayable suspension that dries to leave a smooth film. Such films rapidly disintegrate in aqueous media at a rate that is independent of pH and film thickness.

Actives

[0045] The pharmaceutically active compounds useful in the practice of the present invention include antihistamines, decongestants, antitussives and/or expectorants. Other

actives for use with the present invention include, but are not limited to: non-steroidal anti-inflammatory drugs (NSAIDs) and other analgesic drugs such as acetominophen and phenacetin. These materials are incorporated into the immediate or controlled release formulations of the invention in amounts governed by the desired release characteristics of the material in such excipient base and such that conventional dosages comply with applicable FDA or other regulations.

[0046] Decongestants useful with the present invention (along with a salt form) are phenylephrine (bitartrate, tannate, HBr, HCl), phenylpropanolamine (HCl) and pseudoephedrine (HCl). Furthermore, a number of herbal and/or natural decongestants are known in the art, all of which may be used with the present invention.

[0047] Expectorants for use with the present invention include, e.g., guaifenesin, terpin hydrate, (glyceryl guaiacolate), potassium (iodide, citrate) and potassium guaicolsulfonate. Other expectorants, whether individual ingredients or combinations of ingredients may be used with the present invention. Furthermore, a number of herbal and/or natural expectorants are known in the art, all of which may be used with the present invention, e.g., Oregano Leaf Extract 25 – 500 mg (which may be a liquid extract), Red Clover 25 - 500 mg, Buckthorn Root 25 – 500 mg, or Fenugreek 25 – 500 mg, or mixtures thereof.

[0048] Examples of antihistamines for use with the present invention (e.g., in salt form) are chlorpheniramine (maleate), brompheniramine (maleate), dexchlorpheniramine (maleate), dexbrompheniramine (maleate), triprolidine (HCl), diphenhydramine (HCl), doxylamine (succinate), tripelennamine (HCl), cyproheptatine (HCl), bromodiphenhydramine (HCl), phenindamine (tartrate), pyrilamine (maleate, tannate) and azatadine (maleate). Antitussives that may be used with the present invention (with salt form) include: caramiphen (edisylate), dextromethorphan (HBr) and codeine (phosphate, sulfate). A number of herbal and/or natural antihistamines are known in the art, all of which may be used with the present invention.

[0049] Other actives may also be included with the present invention, e.g., non-steroidal anti-inflammatory drugs (NSAIDs) such as propionic acid derivatives; acetic acid

derivatives; fenamic acid derivatives; biphenylcarboxylic acid derivatives; and oxicams. Examples of propionic acid derivatives include: ibuprofen, naproxen, ketoprofen, flurbiprofen, fenoprofen, suprofen, fenbufen, and fluprofen may be mentioned as preferred compounds. Acetic acid derivatives derivatives include: tolmetin sodium, zomepirac, sulindac and indomethacin. Fenamic acid derivatives derivatives include: mefenamic acid and meclofenamate sodium. Diflunisal and flufenisal are biphenylcarboxylic acid derivatives, while oxicams include piroxicam, sudoxicam and isoxicam. Other analgesics for use with the present invention include acetominophen and phenacetin.

[0050] Those skilled in the art will appreciate that any of the foregoing compounds may be used in the form of their pharmaceutically acceptable salt forms, e.g. –carboxylic acids with potassium or sodium counter-ions, and the like. In one example of the present invention, an expectorant (e.g., Gauifenesin DC) is provided at lower doses and is made available immediately for absorption, followed by a lower dose of a decongestant (e.g., phenylephrine) which is release slowly over, e.g., about 1 to 8 hrs. This release profile makes the product more efficacious since the large amount of expectorant begins to break up mucus prior to the time the decongestant is released to provide long acting decongestant activity after mucus breakdown has begun.

[0051] Generally, guaifenesin is present in amounts of about 10 to about 600 milligrams per capsule. Guaifenesin may be present in amounts of 100, 150, 200, 300, 400, 440, 500 or even 600 or more milligrams per capsule. In one example, guaifenesin is present in amounts of about 100 to about 200 milligrams per capsule, with half or less of that amount used in a pediatric form of the formulation.

[0052] In once example, 400 milligrams of gauifenesin are included as an active for immediate release. Guaifenesin is an expectorant that increases the output of phlegm (sputum) and bronchial secretions by reducing adhesiveness and surface tension. The increased flow of less viscous secretions promotes cilliary action and facilitates the removal of mucus. Hence, expectorants such as guaifenesin change a dry, unproductive cough to one that is more productive and less frequent. Guaifenesin, known chemically as 3(2-methoxyphenoxy)-1,2-propanediol, is a crystalline powder soluble in water and

alcohol. It is indicated in the USP Drug information as an expectorant for the symptomatic relief of cough due to colds and minor upper respiratory infections.

[0053] Phenylephrine may be present in amounts of between about 15 and about 60 milligrams per capsule. Phenylephrine is generally in amounts of about 5 to about 30 milligrams per capsule, with half or less of that amount used in a pediatric form of the formulation.

[0054] In one example of the present invention, phenylephrine is provided in the amount of about 15 mg for extended release. Phenylephrine hydrochloride is an orally effective nasal decongestant. Chemically it is (S)-3-hydroxy-α[(methylamino) methyl] benzenemethanol hydrochloride. Phenylepherine is a synthetic, optically active sympathomimetic amine that has one hydroxyl group on the benzene ring. The hydroxyl group is placed in the position meta to the aliphatic side chain. The meta position affords optimal activity and phenylepherine (neo-synephrine) replaced an older preparation, synephrine, in which the hydroxyl was in the para position.

[0055] Phenylephrine hydrochloride is available in the form of the levorotatory isomer, a white, odorless, non-hygroscopic, crystalline compound possessing a bitter taste. Phenylephrine hydrochloride has a melting point of 140-145 degrees C and is freely soluble in water and alcohol. Decongestant compounds in the form of their free bases as well as their salts, e.g., hydrochloride, citrate, maleate, tannate, etc., are well known.

[0056] Dextromethorphan may be present in amounts of between about 5 and about 20 milligrams per capsule, with a general range of about 10 to about 15 milligrams per caspule. Brompheniramine may be present in amounts of between about 0.5 and about 4.0 milligrams per capsule with a general range of about 2.0 milligrams per capsule. Half or less of that amount may be used in a pediatric form of the formulation.

[0057] Analgesics, e.g., acetaminophen may be present in amounts of up to about 600 milligrams per capsule. Generally, acetaminophen is present in amounts of about 50 to about 200 milligrams per capsule. Ibuprofen may be present in amounts of up to about 150 milligrams, with a range of about 50 and about 150 milligrams per capsule being

used generally. Half or less of that amount may be used in a pediatric form of the formulation.

[0058] Naproxen may be present in amounts of about 50 to about 250 milligrams per capsule, however, naproxen is used generally in amounts of between about 100 and about 150 milligrams per capsule.

[0059] Excipients for use with the present invention are well known to those of skill in the art and include humectants such as glycerin and propylene glycol, preservatives such as sodium benzoate and paraben, sweeteners such as sodium saccharin, corn syrup and sorbitol solutions, menthol and various flavoring and coloring agents. The pharmaceutically active compounds and excipients for human use should be of N.F. or U.S.P. grade.

In-Actives

[0060] Sugar Spheres: Sugar spheres are used as inert cores in capsule and tablet formulations particularly multiparticulate sustained release formulations and are provided in amounts sufficient to accept the active ingredient for extended release, e.g., phenlyepherine. Sugar spheres are generally of relatively uniform diameter and contain 62.5% - 91.5% sucrose with the remainder being starch.

[0061] Pharmaceutical Glaze: (4.5 mg) Shellac is a natural occurring material, consisting of a complex mixture of constituents. The main component of shellac (~95%) is a resin that upon mild basic hydrolysis gives a mixture of compounds of high plasticity. Shellac is used extensively in the pharmaceutical industry as a film coating agent for beads and tablets.

Substrates

[0062] The substrate of the compositions of the present invention may be a powder or a multiparticulate, such as a granule, a pellet, a bead, a spherule, a beadlet, a microcapsule, a millisphere, a nanocapsule, a nanosphere, a microsphere, a platelet, a minitablet, a tablet or a capsule. A powder constitutes a finely divided (milled, micronized, nanosized, precipitated) form of an active ingredient or additive molecular aggregates or a

compound aggregate of multiple components or a physical mixture of aggregates of an active ingredient and/or additives. Such substrates may be formed of various materials known in the art, such as, for example: sugars, such as lactose, sucrose or dextrose; polysaccharides, such as maltodextrin or dextrates; starches; cellulosics, such as microcrystalline cellulose or microcrystalline cellulose/sodium carboxymethyl cellulose; inorganics, such as dicalcium phosphate, hydroxyapitite, tricalcium phosphate, talc, or titania; and polyols, such as mannitol, xylitol, sorbitol or cyclodextrin.

[0063] It should be emphasized that a substrate need not be a solid material, although often it will be a solid. For example, the encapsulation coat on the substrate may act as a solid "shell" surrounding and encapsulating a liquid, semi-liquid, powder or other substrate material. Such substrates are also within the scope of the present invention, as it is ultimately the carrier, of which the substrate is a part, which must be a solid.

Excipients

[0064] The solid pharmaceutical compositions of the present invention may include optionally one or more additives, sometimes referred to as additives. The excipients may be contained in an encapsulation coat in compositions, which include an encapsulation coat, or can be part of the solid carrier, such as coated to an encapsulation coat, or contained within the components forming the solid carrier. Alternatively, the excipients can be contained in the pharmaceutical composition but not part of the solid carrier itself.

[0065] Suitable excipients are those used commonly to facilitate the processes involving the preparation of the solid carrier, the encapsulation coating, or the pharmaceutical dosage form. These processes include agglomeration, air suspension chilling, air suspension drying, balling, coacervation, comminution, compression, pelletization, cryopelletization, extrusion, granulation, homogenization, inclusion complexation, lyophilization, nanoencapsulation, melting, mixing, molding, pan coating, solvent dehydration, sonication, spheronization, spray chilling, spray congealing, spray drying, or other processes known in the art. The excipients may also be pre-coated or encapsulated, as are well known in the art.

Solubilizers

[0066] The pharmaceutical compositions of the present invention may include optionally one or more solubilizers, i.e., additives to increase the solubility of the pharmaceutical active ingredient or other composition components in the solid carrier. It has been recognized by the present inventors that guaifenesin, in fact, acts as a solubilizer for phenylephrine, and is used as such in the examples provided herein. Other solubilizers are known in the art. Mixtures of solubilizers are also within the scope of the invention and are readily available from standard commercial sources.

[0067] The amount of solubilizer that may be included in compositions of the present invention is not particularly limited. Of course, when such compositions are administered to a patient, the amount of a given solubilizer is limited to a bioacceptable amount, which is readily determined by one of skill in the art. In some circumstances, it may be advantageous to include amounts of solubilizers far in excess of bioacceptable amounts, for example, to maximize the concentration of active ingredient, with excess solubilizer removed prior to providing the composition to a patient using conventional techniques, such as distillation or evaporation.

Other Additives

[0068] Other additives conventionally used in pharmaceutical compositions may be included, which are well known in the art. Such additives include, e.g.,: anti-adherents (anti-sticking agents, glidants, flow promoters, lubricants) such as talc, magnesium stearate, fumed silica), micronized silica, polyethylene glycols, surfactants, waxes, stearic acid, stearic acid salts, stearic acid derivatives, starch, hydrogenated vegetable oils, sodium benzoate, sodium acetate, leucine, PEG-4000 and magnesium lauryl sulfate.

[0069] Other additives include, binders (adhesives), i.e., agents that impart cohesive properties to powdered materials through particle-particle bonding, such as matrix binders (dry starch, dry sugars), film binders (PVP, starch paste, celluloses, bentonite and sucrose), and chemical binders (polymeric cellulose derivatives, such as carboxy methyl cellulose, HPC and HPMC; sugar syrups; corn syrup; water soluble polysaccharides such as acacia, tragacanth, guar and alginates; gelatin; gelatin hydrolysate; agar; sucrose;

dextrose; and non-cellulosic binders, such as PVP, PEG, vinyl pyrrolidone copolymers, pregelatinized starch, sorbitol, and glucose).

[0070] For certain actives it may be useful to provide buffering agents (or bufferants), where the acid is a pharmaceutically acceptable acid, such as hydrochloric acid, hydrobromic acid, hydriodic acid, sulfuric acid, nitric acid, boric acid, phosphoric acid, acetic acid, acrylic acid, adipic acid, alginic acid, alkanesulfonic acid, amino acids, ascorbic acid, benzoic acid, boric acid, butyric acid, carbonic acid, citric acid, fatty acids, formic acid, fumaric acid, gluconic acid, hydroquinosulfonic acid, isoascorbic acid, lactic acid, maleic acid, methanesulfonic acid, oxalic acid, para-bromophenylsulfonic acid, propionic acid, p-toluenesulfonic acid, salicylic acid, stearic acid, succinic acid, tannic acid, tartaric acid, thioglycolic acid, toluenesulfonic acid and uric acid, and where the base is a pharmaceutically acceptable base, such as an amino acid, an amino acid ester, ammonium hydroxide, potassium hydroxide, sodium hydroxide, sodium hydrogen carbonate, aluminum hydroxide, calcium carbonate, magnesium hydroxide, magnesium aluminum silicate, synthetic aluminum silicate, synthetic hydrotalcite, magnesium aluminum hydroxide, diisopropylethylamine, ethanolamine, ethylenediamine, triethanolamine, triethylamine, triisopropanolamine, or a salt of a pharmaceutically acceptable cation and acetic acid, acrylic acid, adipic acid, alginic acid, alkanesulfonic acid, an amino acid, ascorbic acid, benzoic acid, boric acid, butyric acid, carbonic acid, citric acid, a fatty acid, formic acid, fumaric acid, gluconic acid, hydroquinosulfonic acid, isoascorbic acid, lactic acid, maleic acid, methanesulfonic acid, oxalic acid, para-bromophenylsulfonic acid, propionic acid, p-toluenesulfonic acid, salicylic acid, stearic acid, succinic acid, tannic acid, tartaric acid, thioglycolic acid, toluenesulfonic acid, and uric acid.

[0071] In some formulations additives may also include: chelating agents (such as EDTA and EDTA salts); colorants or opaquants (such as titanium dioxide, food dyes, lakes, natural vegetable colorants, iron oxides, silicates, sulfates, magnesium hydroxide and aluminum hydroxide); coolants (e.g., trichloroethane, trichloroethylene, dichloromethane, fluorotrichloromethane); cryoprotectants (such as trehelose, phosphates, citric acid, tartaric acid, gelatin, dextran and mannitol); and diluents or fillers (such as lactose,

mannitol, talc, magnesium stearate, sodium chloride, potassium chloride, citric acid, spray-dried lactose, hydrolyzed starches, directly compressible starch, microcrystalline cellulose, cellulosics, sorbitol, sucrose, sucrose-based materials, calcium sulfate, dibasic calcium phosphate and dextrose).

[0072] Yet other additives may include disintegrants or super disintegrants; hydrogen bonding agents, such as magnesium oxide; flavorants or desensitizers; ion-exchange resins, such as styrene/divinyl benzene copolymers, and quaternary ammonium compounds; plasticizers, such as polyethylene glycol, citrate esters (e.g., triethyl citrate, acetyl triethyl citrate, acetyltributyl citrate), acetylated monoglycerides, glycerin, triacetin, propylene glycol, phthalate esters (e.g., diethyl phthalate, dibutyl phthalate), castor oil, sorbitol and dibutyl seccate; and preservatives, such as ascorbic acid, boric acid, sorbic acid, benzoic acid, and salts thereof, parabens, phenols, benzyl alcohol, and quaternary ammonium compounds.

[0073] It should be appreciated that there is considerable overlap between the above-listed additives in common usage, since a given additive is often classified differently by different practitioners in the field, or is commonly used for any of several different functions. Thus, the above-listed additives should be taken as merely exemplary, and not limiting, of the types of additives that can be included in compositions of the present invention. The amounts of such additives may be readily determined by one skilled in the art, according to the particular properties desired.

Processes

[0074] The compositions of the present invention can be prepared by a variety of processes to apply an encapsulation coat onto a substrate or to form a substrate-free solid carrier such as a multiparticulate or a powder. The most commonly used coating and pelletization processes include: balling, spheronization, extrusion, spray congealing, spray drying, pan coating, fluidized bed coating, melt extrusion, crystallization, cryopelletization, nanoencapsulation, coacervation, etc. One skilled in the art will recognize that appropriate additives may also be introduced to the composition or during

the processes to facilitate the preparation of the solid carrier or the dosage forms, depending on the need of the individual process.

[0075] A coating process frequently involves spraying a coating solution onto a substrate. The coating solution can be a molten solution of the encapsulation coat composition free of a dispersing medium. The coating solution may also be prepared by solubilizing or suspending the composition of the encapsulation coat in an aqueous medium, an organic solvent, a supercritical fluid, or a mixture thereof. At the end of the coating process, the residual dispersing medium can be further removed to a desirable level using appropriate drying processes, such as vacuum evaporation, heating, freeze drying, etc.

[0076] A pelletization process typically involves preparing a molten solution of the composition of the solid carrier or a dispersion of the composition of the solid carrier solubilized or suspended in an aqueous medium, an organic solvent, a supercritical fluid, or a mixture thereof. Such solution or dispersion is then passed through a certain opening to achieve the desired shape, size, and other properties. Similarly, appropriate drying processes may be used to control the level of the residual dispersing medium, if necessary. The processes described above, the combination of the processes, or the modification of the processes are well know in the art. Some of the processes are briefly described herein for reference.

Balling

[0077] In a broad sense, pellets are very much like granules and bead; the techniques for producing pellets may also produce granules, beads, etc. Pellets, granules or beads are formed with the aid of, e.g., a pelletizer, a spheronizer or an extruder. The pelletizer, spheronizer or extruder is able to form approximately spherical bodies from a mass of finely divided particles continuously, by a rolling or tumbling action on a flat or curved surface with the addition of a liquid.

[0078] Pelletizers are generally classified based on the angle of their axis as a horizontal drum or an inclined dish pelletizer. Rotary fluidized granulators may also be used for pelletization. A standard fluidized drier bowl may be replaced with a rotating plate as an air distributor. For granulation, a binder liquid is sprayed from via one or two binary

nozzles located axially to the rotational movement of the powder bed. The granulation results in rounding of the granules to approximately spherical pellets. Such balling or agitation techniques are generally influenced by operating conditions, e.g., the bridging/binding liquid requirements, the residence time of the material in the pelletizer, the speed and angle of inclination of the pelletizer, the amount of material fed to the pelletizer and the choice and levels of binder, etc. Those skilled in the art may adjust readily such factors to produce a satisfactory product.

[0079] The choice of binder for a given application may also be determined readily by those skilled in the art. Generally, the binder must be capable of wetting the surfaces of the particle being pelletized or granulated. In general, binders must have sufficient wet strength to allow agglomerates to be handled and sufficient dry strength to make them suitable for their intended purposes. Each process, however, makes use of a different system of forces and may require a different agglomerate strength. The final selection of the binder is made generally based on the type of equipment used. Factors that affect the equipment and binder choices include: the size and size distribution of pellets, bulk density, strength and flow properties. Other factors that affect the performance of the pellets, which may be adjusted by one skilled in the art by the inclusion of additives, choice of equipment and processing conditions.

[0080] EXAMPLES

[0081] Capsule shells and process: 7.5% phenylephrine immediate release beads where used as starting material. A portion of this lot was transferred to a rotating pan. Phenylephrine was added to the beads using of pharmaceutical glaze. The beads were then allowed to roll and cure for 6 hours before sustained release coating was added. In-order to develop the product, four different levels of sustained release coating amounts were added. In one example, 10.93 Kgs of phenylephrine were added to the beads using 4.32 Kgs of pharmaceutical glaze. The beads were then allowed to roll and cure for 6 hours before sustained release coating was added.

[0082] In order to develop the product four different levels of sustained release coating amounts were added. The first was 7.15 kg's of SR mix #1 and 4.96 kg's of

pharmaceutical glaze. Once this loading was complete 5.0 kg's were removed for drying and testing. The second load consisted of 4.75 kg's of SR mix #1 and 2.68 kg's of pharmaceutical glaze. Again 5.0 kg's of beaded material was removed for drying at 40° C and testing. The third load consisted of 5.92 kg's SR mix #1 and 3.43 kg's of glaze. After application another 5.0 kg's of beaded material was removed from the pan for drying at 40° C and testing. The fourth and final load consisted of 7.78 kg's of SR mix #1 and 4.56 kg's of pharmaceutical glaze. The entire pan was allowed to roll and cure under heat lamps for 6 hours before sampling for study.

[0083] Below is a list of all theoretical percentages and actual assay results for the, above, described material.

SR Mix	Theoretical PEH %	Actual PEH %	Diss. 90 min, 3hr, 6hr
#1	21.6%	20.8%	4.6%, 18.6%, 59.3%
#2	19.8%	19.3%	0.2%, 0.8%, 11.0%
#3	17.8%	17.3%	0.16%, 0.4%, 2.7%
#4	15.5%	15.4%	0.6%, 0.8%, 2.6%

[0084] Based on assay and dissolution profile load #1 was selected for use in further development. The moisture content in load #4 may be higher than those loads dried in the tray drier. This may have contributed to why load #3 and #4 have essentially the same dissolution profile despite the increased SR mix. The gauifenesin DC 95% was compressed into slugs using a bb2 type tablet press with standard ¼" cup tooling. GRA001 was pressed into slugs weighing 220 mg each. Capsules were filled using 75 mg of Load #1 beads (15 mg phenylephrine). Then two 220 mg slugs of Gauifenesin DC. These capsule were then placed in a 75 cc bottle and conditioned at 35° C for 24 hours. Dessicant was then added. The material was capped and the induction seal was activated. The material was placed on accelerated stability.

[0085] Dissolution: The present inventors found that the dissolution rate of the phenylephrine is accelerated when combined with Gauifenesin DC. Due to this effect the testing of the dissolution rate is achieved by first making a mock-up of the finished product. By doing so the suitability of the phenylephrine beads was determined more accurately. Direct specifications for dissolution were determined once data was collected to accurately predict this rate change.

[0086] Stability: Capsules were studied for stability. Accelerated stability indicates that the product is stable. Gauifenesin DC released 100% immediately with stable potency. The phenylephrine exhibited a first order release profile consistent with an 8 hour product and was consistent from month to month. Results are summarized below.

Lot #	Count	Container	Closure	Desiccant
DEV 191	100	CON014	CLO452	DES101

Time	GFN Diss. 90 min / Assay	PEH Diss. 90 min / 3 hr / 6 hr	PEH Assay
Initial	103.7% / 99.8%	30.1% / 43.5% / 70.5%	105.2%
4 week	103.5% / 98.5%	33.8% / 49.4% / 78.7 %	105.7%
6 week	104.2% / 98.7%	20.8% / 38.3% / 70.6%	100.4%
8 week	102.6% / 99.5%	26.8% / 44.5% / 78.7%	107.3%
10 week	103.9% / 99.4%	31.5% / 46.2% / 73.1%	97.8%
12 week	104.1% / 98.8%	33.7% / 51.0% / 85.5%	107.7%

[0087] Equipment: Bosch GKF 700 and GKF 2000 machines were used for the pellet and powder functions. The GKF 700 runs the 400/15 product that requires the beads to be dosed prior to powder. The GKF 2000 runs product 200/7.5 and is capable of filling powder followed by beads. The reason for this is that the 400/15 product is in a size 0 elongated capsule that is overfilled. If the beads are added after the powder slug they will tend to roll off the slug during capsule closure. This would result in poor closure and poor content uniformity.

Formula I

[0088] A batch of immediate release first active, e.g., guaifenesin for use with the enveloped formulation was prepared with the following components:

Components	Weight
Guaifenesin DC	421 mg
Talc	5 mg

Formula II

[0089] A batch of immediate release guaifenesin for use with the enveloped formulation was prepared with the following components:

Components	Weight
Guaifenesin DC	632 mg
Talc	3 mg

Stearic Acid	2 mg

Formula III

[0090] A batch of immediate release guaifenesin for use with the enveloped formulation was prepared with the following components:

Components	Weight
Guaifenesin DC	211 mg
Talc	3 mg
Magnesium Stearate	2 mg

Formula IV

[0091] A batch of immediate release guaifenesin for use with the enveloped formulation was prepared with the following components:

Components	Weight
Guaifenesin DC	421 mg
Magnesium Stearate	3 mg
Ludipress	50 mg

Formula IV

[0092] A batch of effervescent first active for immediate release, e.g., guaifenesin for use with the enveloped formulation was prepared with the following components:

Components	Weight
Guaifenesin DC	421 mg
Talc	5 mg
Sodium bicarbonate	25 mg

[0093] When combining the first and the second active, these may be formulated as follows. A capsule for immediate release of a first active and extended release of a second active in an enveloped formulation, in a single capsule:

First Active	**Weight**	**Second Active**	**Weight**
Guaifenesin DC	421 mg	Phenylephrine	15 mg
Talc	5 mg	Bead	44 mg
		Lacquer	6 mg
		Talc	5mg
		Calcium Stearate	5 mg
Capsule	1		

[0094] A formulation for immediate release of a first active and extended release of a second active in an enveloped formulation, in a gelcap:

First Active	Weight	Second Active	Weight
Guaifenesin DC	421 mg	Phenylephrine	15 mg
Talc	0 mg	Bead	44 mg
		Lacquer	6 mg
		Talc	5mg
		Calcium Stearate	5 mg
Gelcap	1		

[0095] A formulation for immediate release of a first active and extended release of a second active in an enveloped formulation, in a suppository:

First Active	Weight	Second Active	Weight
Guaifenesin DC	421 mg	Phenylephrine	5 mg
Talc	5 mg	Bead	15 mg
		Lacquer	2 mg
		Talc	1.5mg
		Calcium Stearate	1.5 mg
Stearic Acid	2 mg		
beeswax/glycerol	1-2 gr		

[0096] An effervescent tablet for immediate release of a first active and extended release of a second active in an enveloped formulation, in an effervescent tablet:

First EffervescentActive	Weight	Second Active Mincap		Weight
Guaifenesin DC	421 mg	Phenylephrine	15 mg	
Talc	5 mg	Bead	44 mg	
		Lacquer	6 mg	
		Talc	5 mg	
		Calcium Stearate	5 mg	
Monosodium citrate	10 mg			
Sodium bicarbonate	10 mg			

[0097] For immediate release of a first active and extended release of a second active in an enveloped formulation one may add the following ingredients, in a caplet:

First Active	Weight	Second Active	Weight
Guaifenesin DC	421 mg	Phenylephrine	15 mg
Talc	3 mg	Bead	44 mg
		Lacquer	6mg
		Talc	5 mg
		Calcium Stearate	5 mg

[0098] To summarize the Examples, the first and second actives may be provided as found in the following table (all amounts in milligrams unless otherwise indicated) and are exclusive of in-actives:

Second Active →	antihistamine	antitussive	expectorant	NSAID	nonNSAID
First Active ↓					
Guaifenesin 100 – 800	1.25 - 200	2.5 - 1000	100 - 800	100 - 750	2.5 - 1000
terpin hydrate, (glyceryl guaiacolate), potassium (iodide, citrate) 100 - 600	1.25 - 200	2.5 - 1000	100 - 800	100 - 750	2.5 - 1000
potassium guaicolsulfonate 100 - 800	1.25 - 200	2.5 - 1000	100 - 800	100 - 750	2.5 - 1000
Oregano Leaf Extract 25 - 500	1.25 - 200	2.5 - 1000	100 - 800	100 - 750	2.5 - 1000
Red Clover 25 - 500	1.25 - 200	2.5 - 1000	100 - 800	100 - 750	2.5 - 1000
Buckthorn Root 25 – 500	1.25 - 200	2.5 - 1000	100 - 800	100 - 750	2.5 - 1000
Fenugreek 25-500	1.25 - 200	2.5 - 1000	100 - 800	100 - 750	2.5 - 1000
Linden - 25-500 Eucalyptus - 25-500 Red Poppy Flowers - 10-100 Licorice – 10 - 100	1.25 - 200	2.5 - 1000	100 - 800	100 - 750	2.5 - 1000

[0099] While this invention has been described in reference to illustrative embodiments, this description is not intended to be construed in a limiting sense. Various modifications and combinations of the illustrative embodiments, as well as other embodiments of the invention, will be apparent to persons skilled in the art upon reference to the description. It is therefore intended that the appended claims encompass any such modifications or embodiments.